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From submolecular biology to submolecular medicine The legacy of Albert Szent-Györgyi

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Abstract

The legacy of Professor Albert Szent-Györgyi is best summarized, by himself, in the mid 20th Century.

"The distance between those abstruse quantum mechanical calculations and the patient bed may not be as great as believed"

We know that his prophetic vision has not been fulfilled as yet; the time is yet to come, perhaps in the 21st Century, when his legacy will be practiced on a daily basis. It may take several generations before we can walk that proverbial short distance from our research computer to the patient bed. It will probably require a 'Grande Armée' of researchers covering the whole spectrum of Mathematics, Physics, Computer Science, Chemistry, Biochemistry, Biology and Medicine, fighting a constant uphill battle in order convert Szent-Györgyi's legacy to reality. In contrast to our present daily practice with our future eschatological hope, the current situation is reviewed and the future direction of the overall process is outlined that shows the progression from Classical Medicine through Molecular Medicine all the way to Submolecular or Quantum Medicine.

Keywords: Albert Szent-Györgyi; Molecular medicine; Citric acid cycle

1. A tribute to Albert Szent-Györgyi

The title of this paper refers explicitly to the legacy of Professor Albert Szent-Györgyi, (Fig. 1), whom we are celebrating with the present *Special Issue*, on his 110th birthday. Some legacies are short in duration and easy to unfold, but this one is different.

His legacy is more than just a legacy. It is, in fact, a scientific prophecy and it will take most, if not all, of the 21st Century to fulfill it as he formulated in the 1950s and published in 1960 [1]:

> "The distance between those abstruse quantum mechanical calculations and the patient bed may not be as great as believed"

This quote summarizes the essence of the prophetic legacy of Albert Szent-Györgyi in the most profound way.

It is hard to speak after the Prophet has spoken! Our basic problem with this prophetic legacy of Szent-Györgyi is that it takes several generations to walk that proverbial short distance from the research computer to the patient bed.

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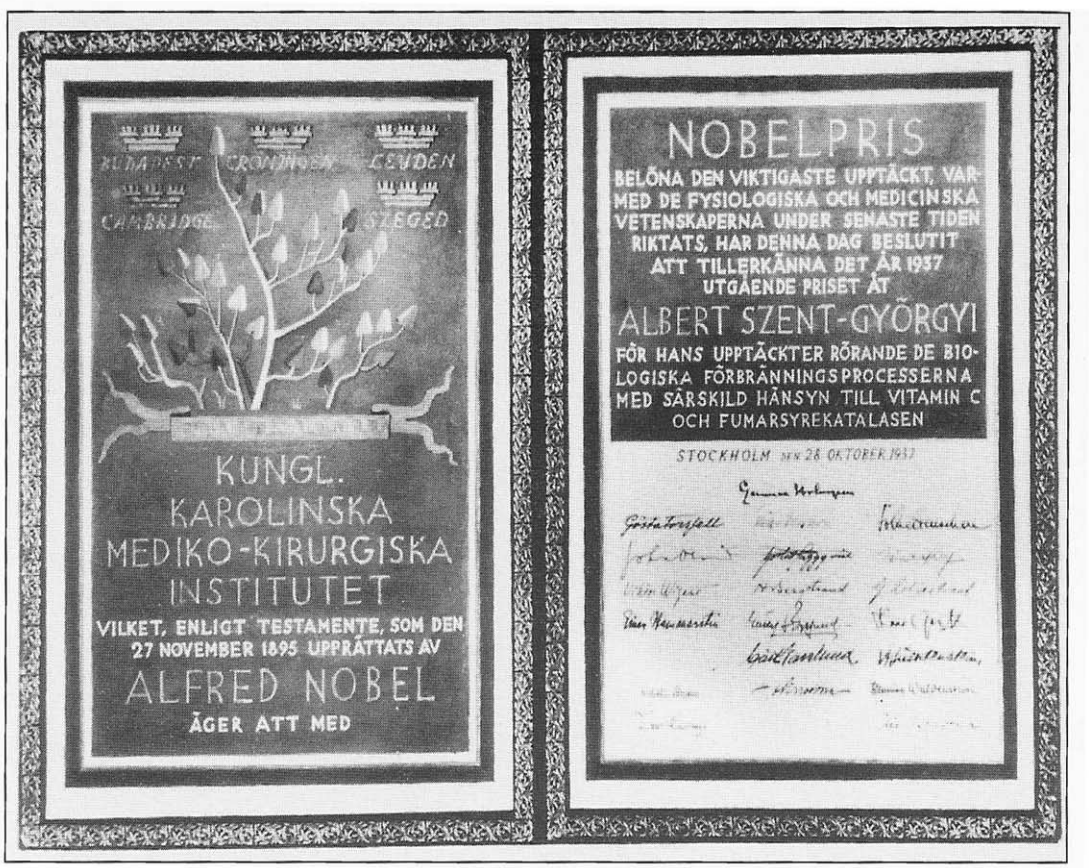


Fig. 1. Nobel prize and portrait of Szent Györgyi.

Consequently, my task is not easy. I am expected to cover the territory not only for our own generation but for the next generation as well, to say the least. In other words, I need to contrast our present daily practice with our future eschatological hope. Thus, while I need to talk about our current battles at the research front, I also need to encourage our younger colleagues to pick up the flag when we cannot carry it any further.

The Nobel Prize was awarded to Professor Albert Szent-Györgyi in 1937 for deciphering some of the intricacies of the Citric Acid Cycle (Fig. 2). That cycle is also referred to as the Szent-Györgyi–Krebs cycle in Europe.

This was the first of such biochemical cycles discovered and it has laid the foundation of *Molecular Medicine*. As the result of his pioneering work the conclusion becomes unavoidable, namely, the human body is nothing else than an automatic molecular machine, in which not wheels but molecules are turning and are ultimately responsible for all bodily functions. However, one can go beyond the molecular level to the submolecular or electronic level. From that famous quotation presented above, it was clear that this was Szent-Györgyi's Quest at the middle of the 20th Century.

He already foresaw, at that time, the emerging new field of Submolecular or Quantum Medicine. According to lingering stories he was seeking out the help of physicists at the time when neither computer hardware nor software was available. After listening carefully to the Nobel Laureate, the Physicists started to laugh when they discovered that those bioactive molecules contained more than one electron. Cleary, this is the fate of everybody who dares to walk ahead of his time.

Today, a half a Century later, we see the situation a bit more clearly. It has become self-evident that while the thesis of Molecular Medicine is that:

> All diseases start at the molecular level, thus, ultimately, all cures must be achieved at the molecular level

we need to go a level further to reach the submolecular level.

Accordingly, the thesis of *Submolecular Medicine* is that:

> All diseases are the result of some unfavourable electron distribution within the human body, thus ultimately all cures must represent a favourable perturbation on the ill-distributed electron density.

By studying life, at the submolecular or electronic level, utilizing the techniques of Quantum Mechanics, surprising new results may emerge. The practical application of such new knowledge could be far reaching for the Pharmaceutical Industry.

2. Basic principles of submolecular medicine

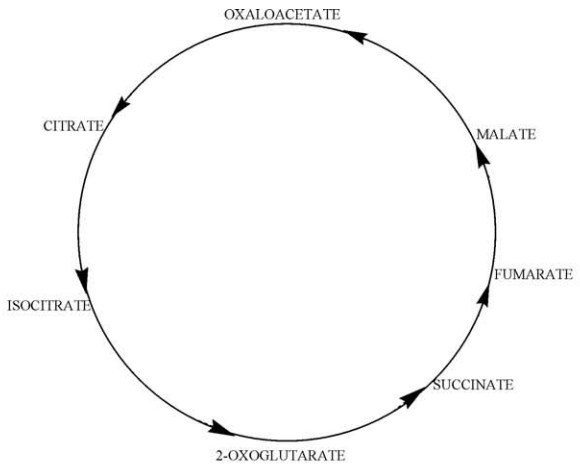
From the composition of the human body (Table 1) it is possible to estimate its content, using only the major components.

For a person, who weighs 100 kg, it is estimated that his body consists of 0.98×10^{28} atomic nuclei and 2.81×10^{28} electrons. While most of this person's weight (over 99.9%) resides within the atomic nuclei, the total volume of these nuclei is much less than a micro micro-litre (μl). Thus, the human body is virtually an empty bag. In contrast to this, the 2.81×10^{28} electrons carry hardly any weight (less than 0.1%). According to the final results of Table 1 (2.81×10^{28}) the total mass for the electrons is calculated to be about 25 g after taking into account Avogadro's number (6.03×10^{23}) and the relative mass of the electron (1/1840):

$$(2.81 \times 10^{28}/6.03 \times 10^{23}) \times (1/1840) = 25.35 \text{ g}$$

Hence, if we consider the human body as a large bag, that is 100 l in volume, it would be filled up by 25 g of electrons behaving as a uniform 'electron gas'. Of course, due to the presence of the atomic nuclei the electron density will not be completely uniform. Rather, it will assume some particular distribution in which it will be relatively high in the vicinity of the atomic nuclei. Also the various organs, like the heart and lungs would exhibit different electron density as may be appropriate for denser and less dense parts.

Virtually an infinite number of possible electron distributions may occur from such a collection of atomic nuclei and electrons. Since only one such, electron distribution can be regarded to represent 'Perfect Health', very similar, or only slightly



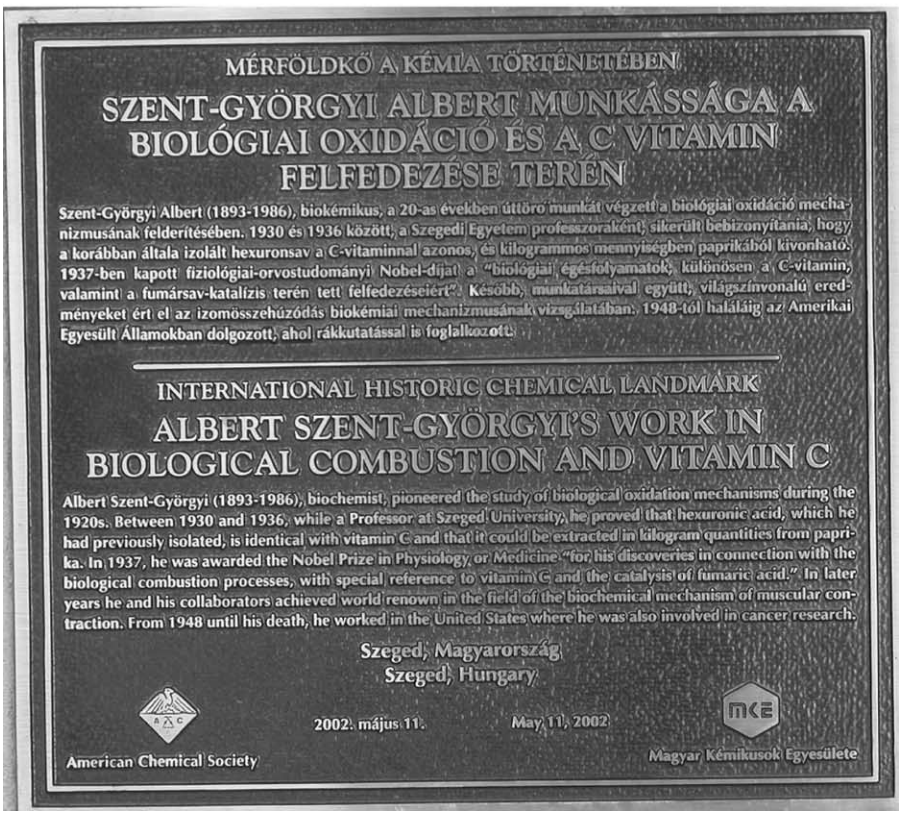


Fig. 2. Szent Györgyi–Krebs biochemical pathway and brass plaque at the University of Szeged.

different, electron distributions must represent very good, but not perfectly healthy, states. This is case for a well-defined margin. As the electron distribution gets further and further away from the ideal or perfect distribution we reach a large collection of ill-distributed electron densities, which are exhibited by people suffering from various diseases. In many cases, when these deviations are located close to the ideal

Table 1
The major components of the human body

	Weight (%)	Gram/100 kg	Mol/100 kg	No. of atoms/100 kg	No. of electrons/100
Oxygen	65	65,000	4062	24497×10^{23}	147717×10^{23}
Carbon	18	18,000	1500	9045×10^{23}	54270×10^{23}
Hydrogen	10	10,000	10000	60300×10^{23}	60300×10^{23}
Nitrogen	3	3000	214	1290×10^{23}	9030×10^{23}
Calcium	1.5	1500	357	215×10^{23}	4300×10^{23}
Phosphorous	1.0	1000	32.3	194×10^{23}	2910×10^{23}
Potassium	0.35	350	875	53×10^{23}	1007×10^{23}
Sulfur	0.25	250	781	47×10^{23}	752×10^{23}
Sodium	0.15	150	652	41×10^{23}	451×10^{23}
Chlorine	0.15	150	395	24×10^{23}	408×10^{23}
Magnesium	0.05	50	200	12×10^{23}	144×10^{23}
Iron	0.0004	–	–	–	–
Iodine	0.00004	–	–	–	–
Total	–	–	–	95721×10^{23}	281289×10^{23}
Rounded Total	–	–	–	0.96×10^{28}	2.81×10^{28}

distribution, the ill-distributed electron density may be forced to move back toward the ideal distribution. This is the reason why the Pharmaceutical Industry is producing 'drugs to cure' for people whose electron distribution has deviated only a little from the ideal distribution. Once the electron distribution can no longer be changed back to normal, i.e. the illness becomes irreversible, death results.

The above information can also be translated to the language of thermodynamics.

The healthy human body is the most organized molecular machine, so its entropy is at its lowest state. When illness strikes, the human body will become less organized internally. So with increasing disorganization, its entropy is on its rise ($\Delta S > 0$). Eventually, at death, entropy reaches its highest value. The opposite trend can be said about the change in Gibbs free energy (ΔG) on going from the healthy body down to the sick body all the way to the dead body ($\Delta G < 0$), as illustrated in Fig. 3.

3. The question of steady-state or virtual stationary electron distribution

The human body is a very complicated molecular machine. A good portion of its activity lays in energy processing and converting the chemical energy of food to biological energy (ATP) in its metabolic machinery. The mitochondria, present practically in all cells, carry out this job in the form of a 'biological fuel cell' (Fig. 4).

In a biological fuel cell, the reductive and oxidative compartments are separated. This is analogous to the cathodic and anodic channels of a regular fuel cell.

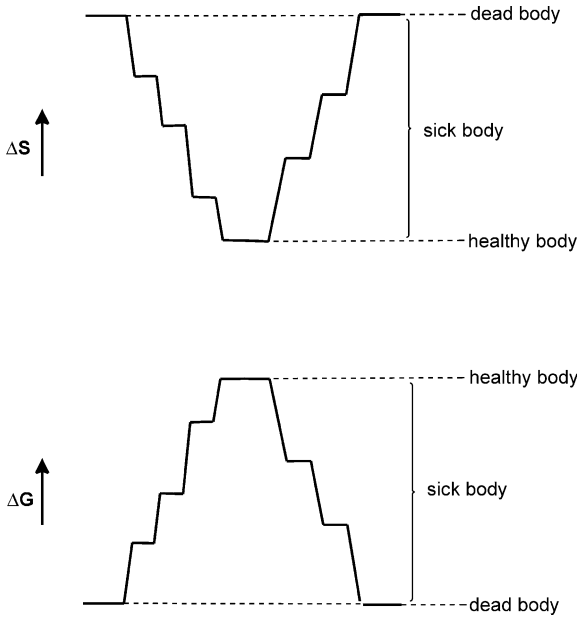


Fig. 3. A schematic illustrations of the key thermodynamic functions (ΔS and ΔG) for the human body in different states.

Of course in the biological fuel cell (i.e. the mitochondria) the electrons are not carried through a piece of wire but are transmitted through hydride ions [:$H^{(-)}$] which are carried by a redox coenzyme such as $NAD^{(+)}$ in the form of NADH. All of these are illustrated in Fig. 4.

Thus the whole human body may be considered as a power-generator consisting of a very large number of biological fuel cells.

The human body not only produces energy for its physical and mental work but must refine its own fuel through its digestive system. The body also has to renew itself implying that after the programmed cell-death, the dead cells need to be replaced. It is also necessary to produce offspring for the survival of the species. Both of these processes require genetic information (DNA) and a reproduction mechanism.

The essence of the foregoing is that the human body is a dynamic molecular machine, which is never stationary. Substances enter in the form of food, and exit in the form of excretion. Oxygen is inhaled for the wet-combustion of the refined fuel. Exhaust, in the form of CO_2 and H_2O is exhaled as illustrated in Fig. 5.

Clearly, this molecular machinery is in constant move, perhaps not at constant speed because at night time it is slower and at daytime it is faster. Nevertheless, with all its cycles, including daily as well as monthly (menstrual) ones, one may still consider the human body (even allowing for variations from adulthood to old ages) to be in some steady-state of

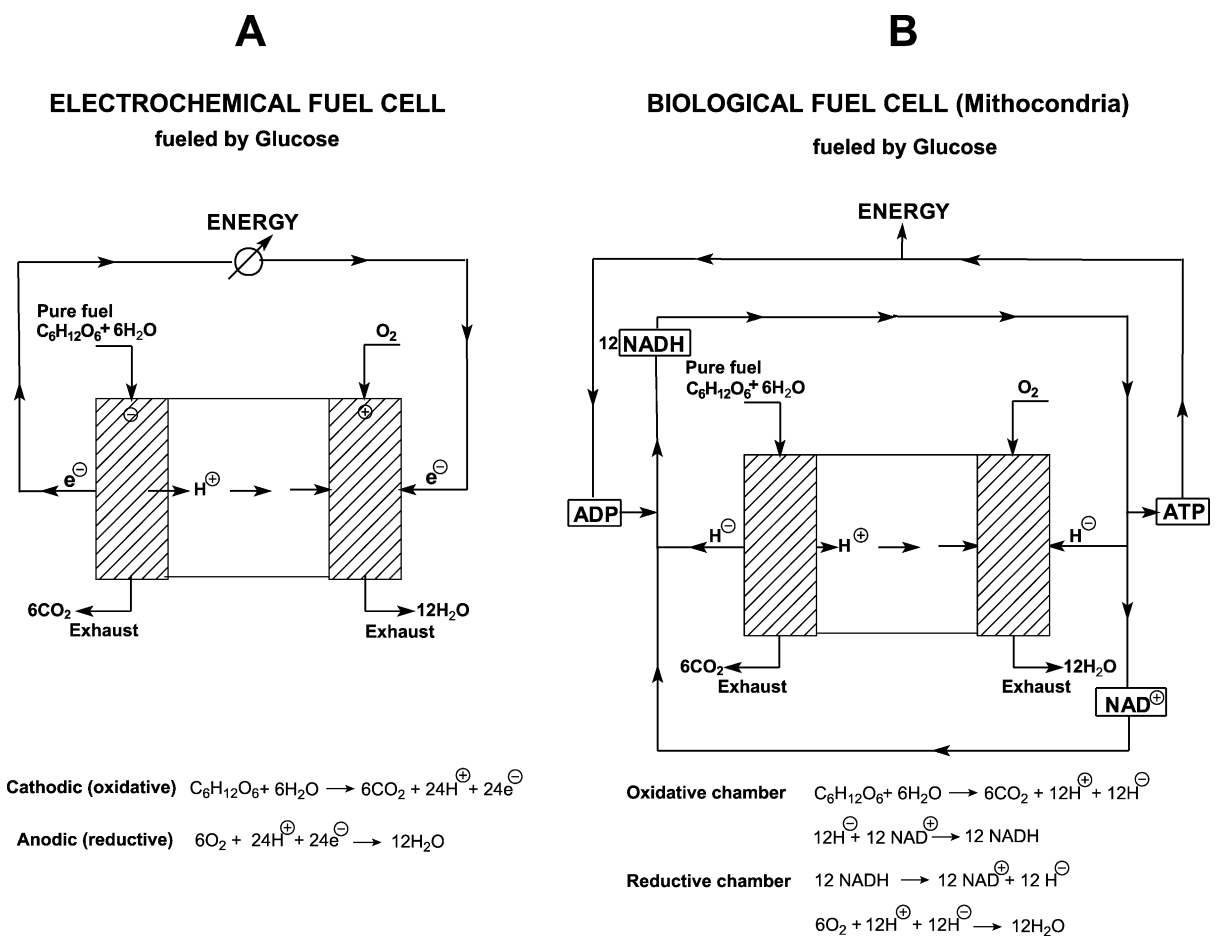


Fig. 4. Fuel cells: electrical (left) and biological (right).

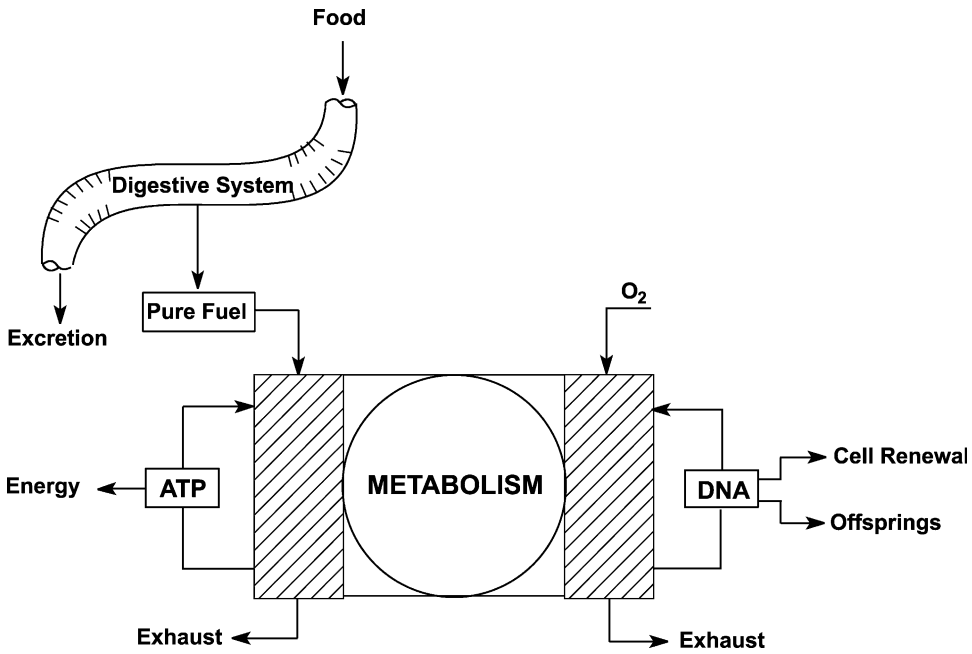


Fig. 5. Human body as a self reproducing machine.

electron distribution. Such steady state of otherwise time dependent electron distribution of the human body is distinctly different when it is healthy from the distribution that may exist when it is sick. Thus, healing at the electronic level may well be considered as the next step for Medicine and the associated Pharmaceutical Industry.

4. The current state of research

Recognizing that the yardstick for human beings is metre and the yardstick for atoms and small molecules is angstrom ($1\ \text{Å} = 10^{-10}$ m) it becomes self evident the nine order of magnitude (i.e. $10\ \text{Å} \times 10^{9} = 1$ m) shift in scale must cover a rather complicated hierarchy. It is not trivial therefore to build the human body from as set of small molecules of the dimension of 10 Å. This biological organization is illustrated in Fig. 6.

The demarcation line, showing computational limit at the dawn of the 21st Century illustrates that we can compute only at the level of Chemistry and Biochemistry but not as yet at the level of Biology.

Speaking of the chemical level, our primary goal is configurations and conformations for molecular structures and mechanism for reactions (Fig. 7). Later, a schematic illustration for one of each of these classes will be given.

As for as Bioactive molecules are concerned some important classes are listed (Fig. 8). The actual number of molecules has no final count.

Since practically the whole periodic table is present in the human body, admittedly some of the elements in rather low concentration, the number of actual molecules must be very large. Computations for many of these bioactive molecules are reported in this volume.

There are, in this volume an unusually large number of papers authored by young researchers. However, if we consider the magnitude of the problems the human body poses even the proverbial Grande Armée would not be large enough to do all the research required. The magnitude of the project ahead of us supersedes the magnitude of the Human Genome project. This means that we need to change policy in our approach to compile a database as large as required for the deciphering the secrets of the human body. The project would get a boost if we were to rely on the millions of undergraduate students of the planet. In the same time those who

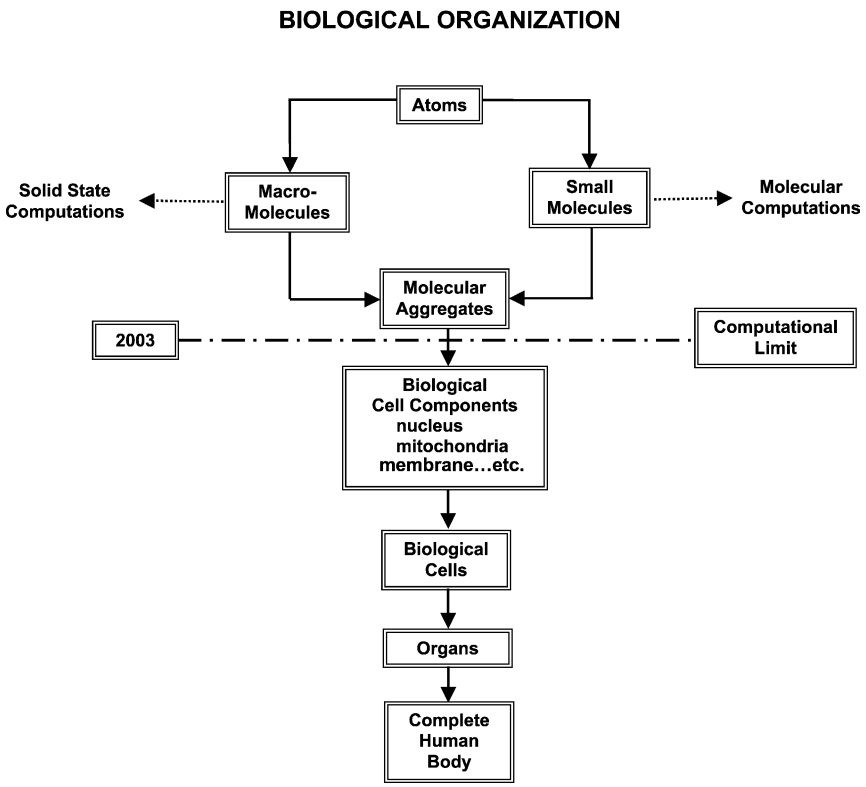


Fig. 6. Biological organization.

were to participate in such research projects would become better graduate students. Professor Kenneth Bartlett wrote a paper in this volume in which he speaks about the integration process of Teaching and Research.

In order to illustrate some of the complexities involved let us briefly consider two topics:

1. Peptide folding
2. Biological methylation

4.1. Peptide folding

The detailed knowledge of peptide folding may be considered to be a prelude to the understanding of

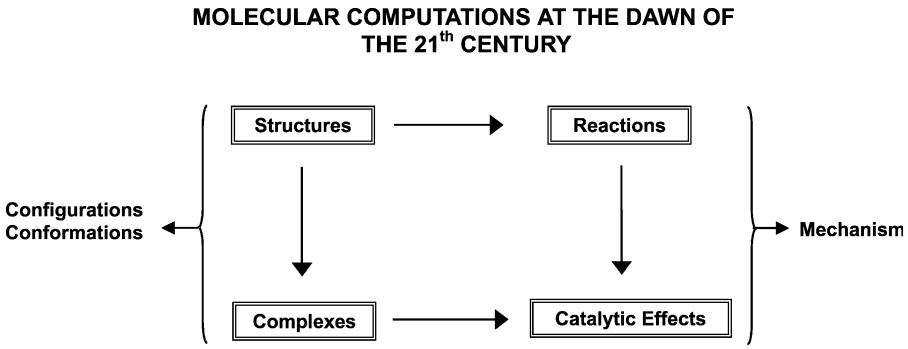


Fig. 7. Computations in the 21st century.

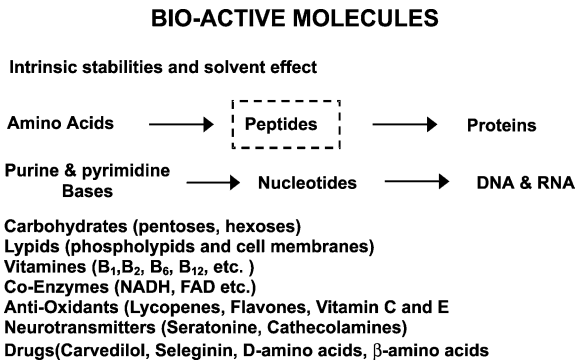


Fig. 8. Bioactive molecules.

protein folding [1,7]. However, even as small a unit such as tetrapeptides represent an astronomical problem (Fig. 9).

Numerous publications testify concerning the complexity of peptide folding [2,3] which is a prelude to the understanding of protein folding [1,3]. The establishment of a conformational database seems to be essential to a successful approach. There are hopes to automate the input generation as well as the tabulation of output results and management of the generated database in the foreseeable future [1,5].

Working with Professor Emil Pai and Michelle Sahai some advances were made in the case of a tetrapeptide project Pro-Pro-Thr-Pro (Fig. 10) [4] by starting with the central dipeptide moiety: Pro-Thr [6]. This will form the basis of the design of an anti-bacterial drug which protects immunoglobulin A (IgA) against bacterial proteolytic enzymes.

Multivariable Fourier analysis of potential energy surfaces might eventually lead to analytic functions which could represent Ramachandran type potential energy hypersurfaces describing peptide folding [7].

Finally, it will be inevitable to analyze the entropy change (ΔS) along the Ramachandran map [8] to determine the relative amount of information present in the various conformations associated with the entropy contribution ($-T\Delta S$) to the free energy (ΔG) of peptide folding.

Even though only four small areas are singled out, nevertheless it is abundantly clear that peptide folding in a mega-project. Numerous papers present in this volume will illustrate, more clearly, the depth of the problem at hand.

4.2. Biological methylation

Even though the methyl group is perhaps the smallest function group its biological transfer is very important. There is scattered evidence that in depression methyl transfer does not occur at the level it is required.

MULTITUDES OF PEPTIDE CONFORMATIONS FOR FULLY TRANSPEPTIDES

		Backbone (BB)		Side chain	
Number of Amino acid	Sequences	Number of BB Rotors	Max No. of BB Conformers	Number of SC Rotors	Max No. of SC Conformers
1	20=20	2	$3^2 = 9$	1	$3^1 = 3$
2	20^2=400	4	$3^4 = 81$	2	$3^2 = 9$
3	20^3=8000	6	$3^6 = 729$	3	$3^3 = 27$
4	20^4=160000	8	$3^8 = 6561$	4	$3^4 = 81$

One sequence out of the 160000 sequences:

Thr Val Ser Leu

BB(1)[SC(1)] x BB(2)[SC(2)] x BB(3)[SC(3)] x BB(4)[SC(4)]

9 [9] x 9 [3] x 9 [9] x 9 [9] = $9^4[9^3x3]$ = 6 561 x [2 187] = 14 348 907 conformers

Fig. 9. Peptide conformations.

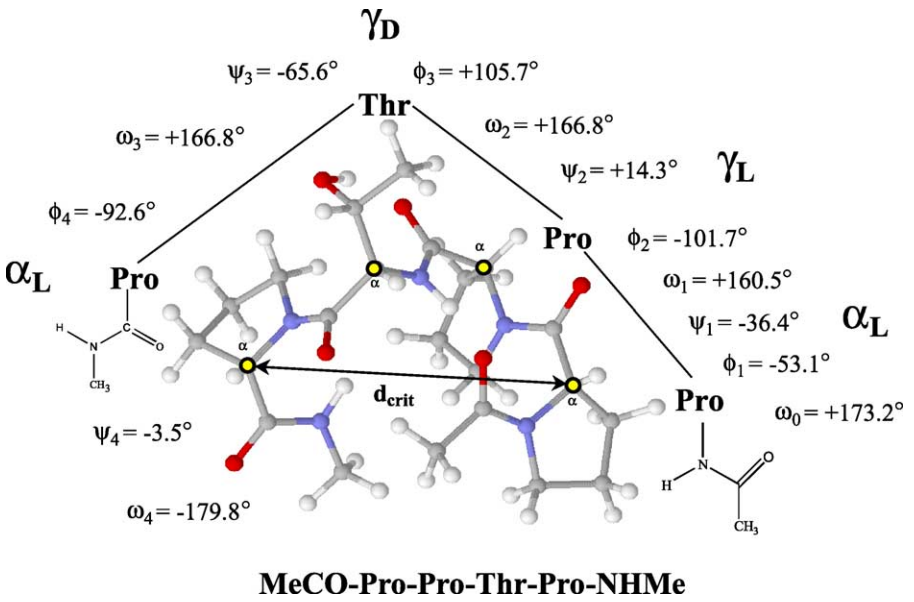


Fig. 10. The IgA tetrapeptide sequence.

Neuro-transmitters are methylated by SAM as illustrated in Fig. 11. In this process, methionine (Met) is converted to homocysteine (Hcy).

The remethylation of homocysteine [9,10] to methionine [11] requires tetrahydrofolate (derivative) which is also shown in Fig. 11. The tetrahydrofolate derivatives [12] involved in C_1 transfer is summarized in Fig. 12.

Papers of numerous young researches are included in this volume which illustrate that although there is a courageous start we have hardly scratched the surface. Thus the road ahead of us is not easy, yet it is very long. We only get comfort from the ancient proverb that 'even the longest journey starts with the first step'.

Before closing, I wish to provide some moral conclusion for the encouragement for our younger colleagues who will carry the burden of this multi-generation project to fulfill Szent-Györgyi's prophetic legacy.

5. Moral conclusions

To turn to the more philosophical aspect of the implications of our research I would like to admit, that most of us like fairy tales. We do like them, because there is more truth in a fairy tale than in reality. Reality tells us how things actually are and fairy tales tell us how things really ought to be. In fairy tales, irrespectively whether it is old or new, it is always the good that wins and the evil looses at the end. Countless examples can be drawn from the literature of the world from the classical 'Snow White and the Seven Dwarfs' to the contemporary 'Star Wars'.

When we examine the great religions of the world we have the impression that the Universe is a battle ground and the war is between good and evil. Such a concept has appeared many times, during the History of Art throughout the centuries.

Many of the undergraduates I have been teaching in Toronto during the years were and are preparing to enter Medical Schools. Most of the professors, from the older generations, tempted to view this with skepticism saying that they want to become Medical Doctors only because of the money. When I asked them why they choose that field most of them told me that they wanted to do something that they consider to be 'doing good'.

Teaching for 40 years I became accustomed to see that most of my students, are in fact, telling the truth. Thus, I am convinced, that in addition to their realism toward money they have a deep-seated conviction that they have to be warriors on the side of good rather

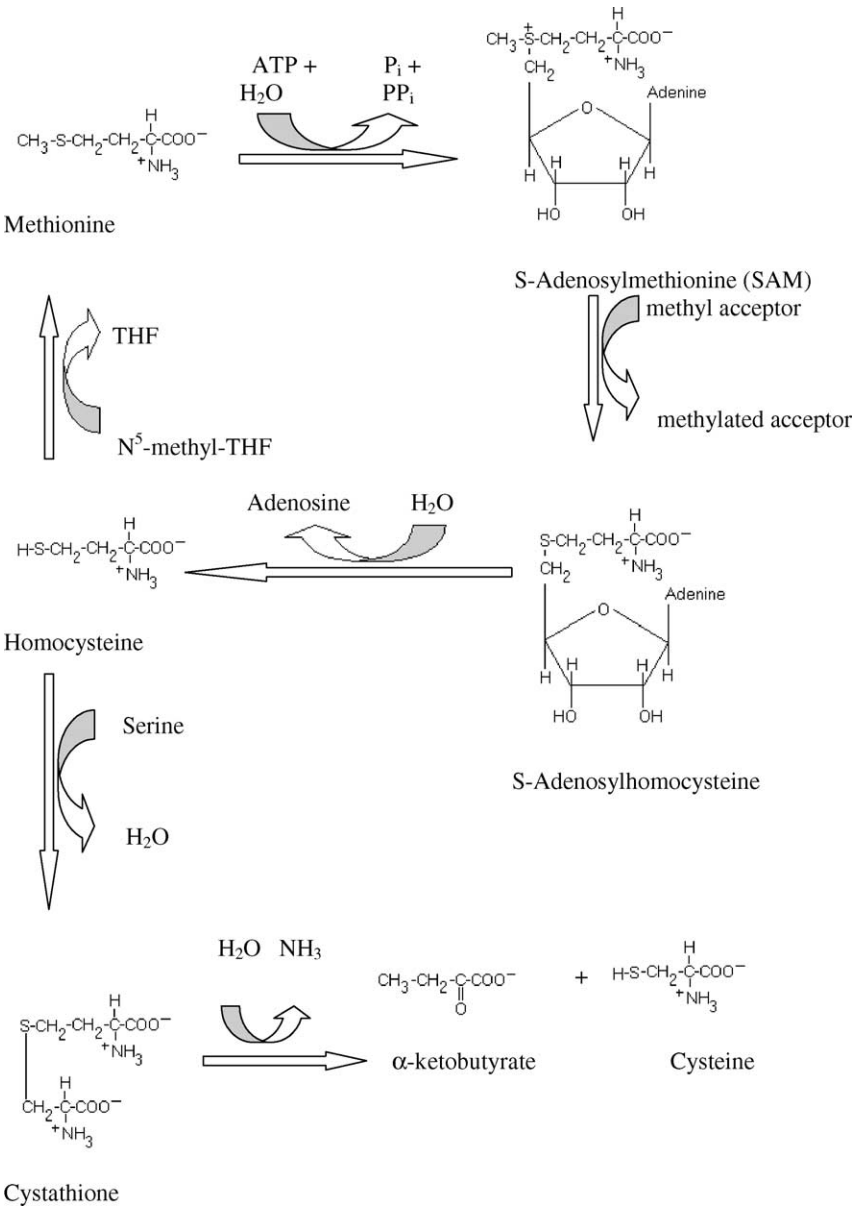


Fig. 11. Methionine cycle.

than on the side of evil while they may not become Dr Schweitzer nevertheless they wish to help in making the world a better place.

When we consider one of the most basis premises of Quantum Mechanics, the 'Uncertainty Principle', we learn that the only way to observe a small object, like an electron, is by carrying out a certain interaction with another particle, like a photon, which leads to some perturbation (Fig. 13).

Thus, by simply observing an electron, we altered the state of the electron. Because the electron is in the Universe we also altered the state of the Universe by virtue of the fact that we altered the state of the electron which is in the Universe. Thus, our action

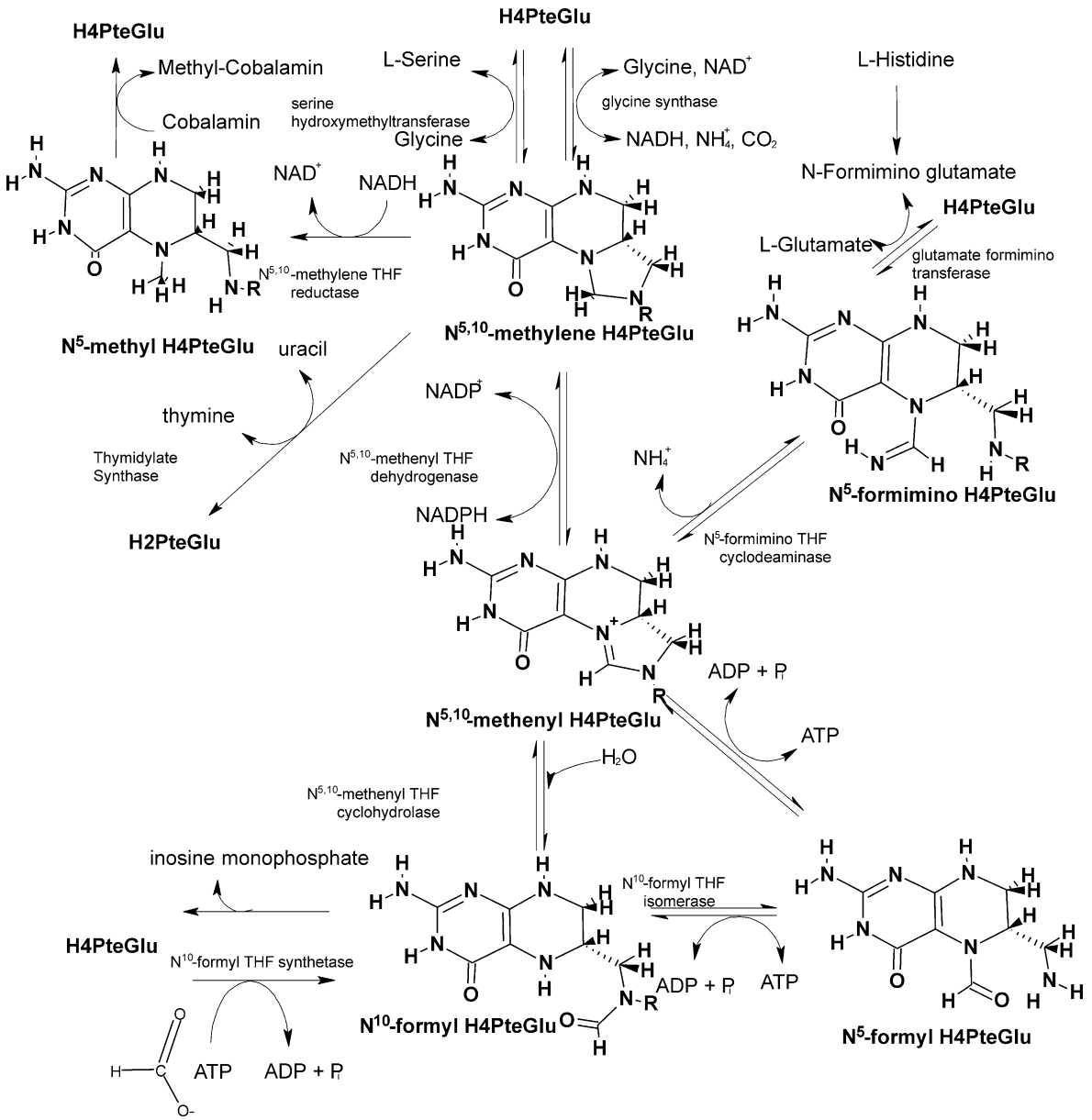


Fig. 12. Tetrahydrofolate derivatives.

does not go unnoticed. This is also true in a general sense. Medical healing, by any therapy, is also a perturbation on the ill-distributed electron density within the human body. As we altered the state of electron distribution in the body of a single human being we also altered the state of the Universe by virtue of the fact that single human being is also within the Universe.

Finally information theory tells us that the increase of information leads to negative entropy change ($\Delta S < 0$). Structures, irrespectively whether it is the structure of galaxies or those of molecules also

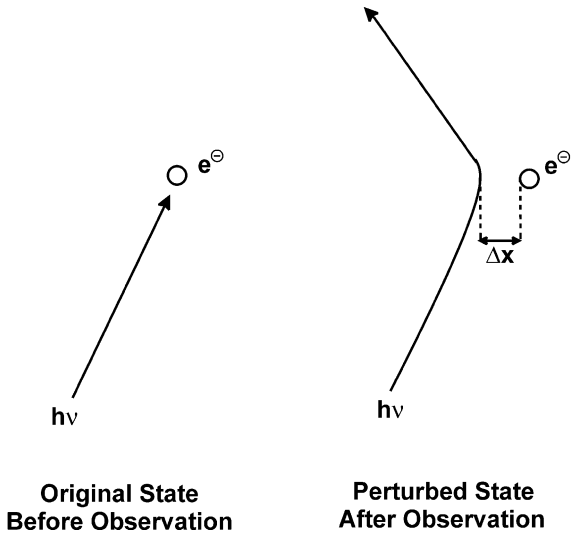


Fig. 13. Observation and uncertainty.

represent information (Fig. 14). Consequently, certain conformational change could in fact reduce or increase the entropy of a molecule and thereby the entropy of the entire Universe. Also, when we administer a drug to form a drug–receptor complex the new structure contains new information and therefore the entropy is expected to be reduced.

So, irrespectively if we start from the higher aspirations of mankind or from the most fundamental science of the human race the conclusion is inescapable; with our actions, we do make a difference in the world because we live in a

"Participatory Universe"

We should have been warned at birth that we are entering into a *Participatory Universe* but perhaps the present warning comes just in time for our young colleagues. At least from now on, they shall be keenly aware that any act that they commit, let it be good or evil, will, in fact, be written into the evolutionary direction of the Universe because we do live in a

"Participatory Universe"

It remains to be seen if at some future date philosophers and theologians will discuss good an evil deeds in terms of negative and positive entropy changes. Nevertheless, today I am highly appreciative of the motivation of my colleagues, who wish to do something good when they plan to enter in to any one of the seven fields that represents a full spectrum of Molecular Science from Mathematics to Medicine (Fig. 15).

I sincerely hope that their own efforts as well as their students' effort will shift the focus of Physicians from Molecular Medicine to Submolecular Medicine in accordance with the legacy of Professor Albert Szent-Györgyi.

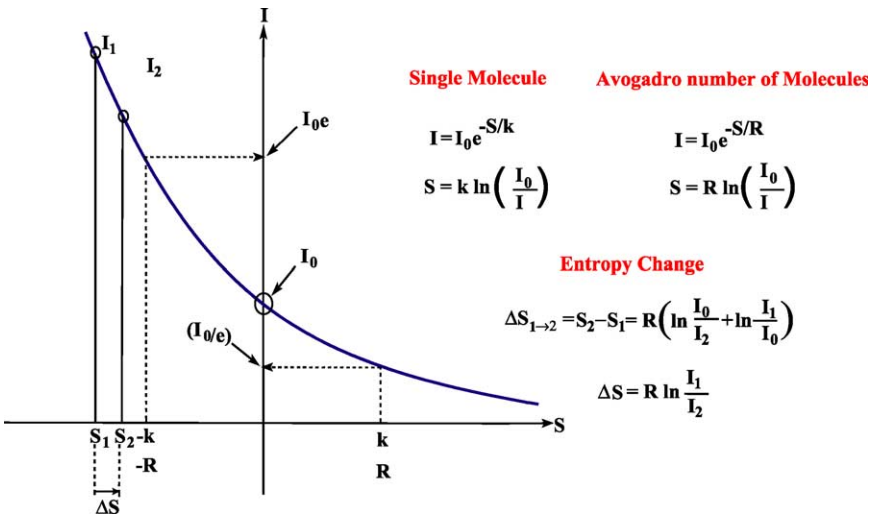


Fig. 14. Entropy and information.

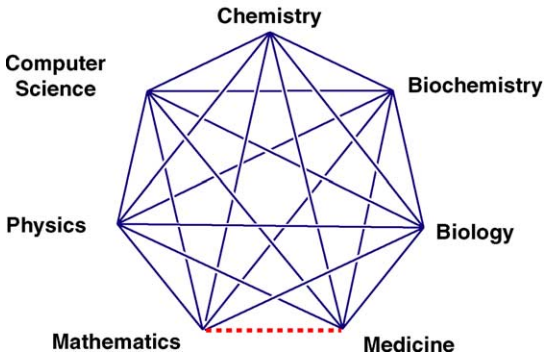


Fig. 15. The seven fields of molecular science.

In closing, I would like to leave for them, for the long road ahead, two encouraging quotations and a warning.

Quotations

Nearly everyone takes the limits of his vision for the limits of the world. A few do not. Join them—Arthur Schopenhauer

We must not be afraid of dreaming the impossible if we want the seemingly impossible to become a reality—Vaclav Havel

Warning

The future usually arrives a little bit sooner than we are ready to give up the present.

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